DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

JOINT MEETING

NONPRESCRIPTION DRUGS ADVISORY COMMITTEE AND PULMONARY - ALLERGY DRUGS ADVISORY COMMITTEE

Friday, May 11, 2001

8:00 a.m.

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P A R T I C I P A N T S

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Alastair Wood, M.D.

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Mark S. Dykewicz, M.D.
Robert J. Fink, M.D.
Jean G. Ford, M.D.
Michael S. Niederman, M.D.

CONSULTANTS:

James Barainuk, M.D. (Non-Voting)
Dan Roden, M.D.

FDA:

Robert Temple, M.D.
Charles Ganley, M.D.
John Jenkins, M.D.
Sandra Kweder, M.D.
Robert Meyer, M.D.

C O N T E N T S

C O N T E N T S (Continued)

P R O C E E D I N G S

Call to Order and Introductions

DR. BRASS: I am going to go ahead and begin the meeting. I am Eric Brass, from Harbor-UCLA Medical Center and Chair of the Nonprescription Drugs Advisory Committee.

Before we begin the official business today, I think we have a large panel and I would just like to go around and allow everybody to introduce themselves. The microphones require you to depress the "speak" button to be heard. Please do not speak without a microphone, and please be sure to turn your microphone off afterwards or we will hear your side bars. George, if you could begin the introductions, please?

DR. BLEWITT: Yes, I am George Blewitt. I am the industry liaison representative for the Nonprescription Drugs Advisory Committee.

DR. BARAINUK: Jim Barainuk, pulmonologist at Georgetown, from the Allergy Pulmonary Committee.

MS. CONNER: I am Brenda Conner. I am the consumer representative to the pulmonary and allergy committee.

DR. KRENZELOK: I am Ed Krenzelok. I am

Director of the Pittsburgh Poison Center and Professor of Pharmacy and Pediatrics at the University of Pittsburgh.

DR. VOLLMER: I am Bill Vollmer. I am a statistician and epidemiologist with the Kaiser Permanente Center for Health Research in Portland, Oregon.

DR. GILLIAM: I am Edwin Gilliam, a nurse practitioner from Tucson, Arizona and on the NDAC committee.

DR. APTER: I am Andrea Apter, University of Pennsylvania. I am an allergy immunologist and I am on the pulmonary allergy committee.

DR. PATTEN: I am Sonia Patten. I am from Minneapolis, Minnesota and I am a consumer representative of the Nonprescription Drugs Advisory Committee.

DR. WOOD: I am Alastair Wood. I am a clinical pharmacologist from Vanderbilt University in Nashville, Tennessee.

DR. RODEN: I am Dan Roden. I am a clinical pharmacologist from Nashville, Tennessee.

DR. JOAD: I am Jesse Joad. I am a pediatric pulmonologist and allergist at the University of California, Davis and I am on the

pulmonary allergy committee.

DR. KELLY: Bill Kelly, University of New Mexico, Department of Pediatrics, clinical pharmacist.

DR. JOHNSON: I am Julie Johnson. I am from the University of Florida College of Pharmacy and Cardiovascular Medicine, and I am on NDAC.

DR. TITUS: I am Sandy Titus. I am the executive secretary for NDAC and I did this meeting jointly with the executive secretary for pulmonary allergy who is Camilla Topper.

DR. UDEN: I am Don Uden, University of Minnesota, member of NDAC.

DR. D'AGOSTINO: Ralph D'Agostino, biostatistician from Boston University, consultant to NDAC.

DR. DYKEWICZ: Mark Dykewicz, in the Division of Allergy and Immunology at St. Louis University School of Medicine, a member of Pulmonary and Allergy Drugs Advisory Committee.

DR. NEILL: I am Richard Neill, a family physician in the Department of Family Practice and Community Medicine from the University of Pennsylvania.

DR. FINK: I am Bob Fink, George

Washington University in Washington, D.C., and a pediatric pulmonologist at Children's National Medical Center.

DR. WILLIAMS: I am Henry Williams, Howard University and member of NDAC.

DR. LAM: I am Francis Lam, from the University of Texas Health Science Center in San Antonio, Department of Pharmacology and Medicine. I am a member of NDAC.

DR. NIEDERMAN: I am Michael Niederman, Pulmonary and Critical Care at Wintrhop Hospital in Mineola, New York, and I am on the faculty of State University of New York at Stonybrook, and I am on the Pulmonary and Allergy Advisory Committee.

DR. CLAPP: I am Leslie Clapp, pediatrician, Main Pediatrics in Buffalo, New York, and Clinical Associate Professor of Pediatrics at State University of New York at Buffalo.

DR. GANLEY: I am Charlie Ganley, the Director of the Division of Over-the-Counter Drugs at FDA.

DR. MEYER: I am Bob Meyer. I am the Director of the Division of Pulmonary Allergy Drugs at FDA.

DR. JENKINS: I am John Jenkins. I am the

Director of the Office of Drug Evaluation II, FDA.

DR. KWEDER: I am Sandra Kweder, FDA.

DR. BRASS: Thank you. I will now ask Dr. Titus to read today's conflict of interest statement.

Conflict of Interest Statement

DR. TITUS: The following announcement addresses the issue of conflict of interest with regard to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda for the meeting and all financial interests reported by the committee participants, it has been determined that all interests in firms regulated by the Center for Drug Evaluation and Research present no potential for an appearance of conflict of interest at this meeting, with the following exceptions. In accordance with 18 USC 208(b), full waivers have been granted to Dr. Ralph D'Agostino, Dr. Eric Brass, Dr. Hari Sachs, Dr. William Kelly, Dr. Andrea Apter, Dr. Michael Niederman and Dr. Dan Roden.

In addition, a limited waiver has been granted to Dr. James Barainuk which allows him to

participate in the discussions without voting. A copy of the waiver statements may be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

In addition, we would like to disclose for the record that Drs. Lam, Sachs, Dykewicz, Barainuk and Williams and Michael Niederman have interests which do not constitute a financial interest within the meaning of 18 USC 208(a) but which could create the appearance of a conflict. The agency has determined, not withstanding these interests, that the interest of the government in their participation outweighs the concern that the integrity of the agency's programs and operations may be questioned. Therefore, Drs. Lam, Sachs, Dykewicz, Barainuk and Niederman may participate fully in today's discussions.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the record.

With regard to all other participants, we

ask in the interest of fairness that they address any current or previous financial involvement with any firm whose products they may wish to comment upon.

DR. BRASS: Thank you very much. I will now ask Dr. Ganley, from the FDA, to give us our introduction for today's session.

Welcome and Introduction to Today's Issues

[Slide]

DR. GANLEY: I would just like to welcome everyone to the meeting today. Before introducing the topic for discussion today, I would just like to thank the members of the Nonprescription Drugs and Pulmonary Drugs Advisory Committees for taking the time from their busy schedules to participate in today's discussion.

I would also like to acknowledge the work of the staff at the FDA involved in the review of material related to the issue for discussion today, and the advisers and consultant staff at the FDA for their efforts in organizing this meeting.

[Slide]

Today's meeting will discuss issues raised in a citizen petition. For those of you who are unfamiliar with this process, the regulations for

citizen petitions are covered in Title 21 of the Code of Federal Regulations, Part 10, specifically Section 10.30. Simply stated, it request that the Commissioner of FDA takes some action.

The other important thing to understand with regard to citizen petitions is that they are submitted to a public docket. Anyone can read them and, if they choose, submit comments to the docket relevant to the petition. These comments will be taken into consideration during the review of the petition.

In reviewing the petition, the Commissioner may hold a hearing, such as the advisory committee meeting being held today. It can also convene meetings, conferences and discussions with persons outside the agency, propose to issue, amend or revoke regulations; publish a Federal Register Notice requesting information, and participate in other public proceedings about the issue.

Citizen petitions raising issues related to the marketing of OTC products are not unique. They more commonly involve products that would be marketed under the OTC monographs and have been discussed at public meetings in the past. This

petition is somewhat unique in that it deals with products that are marketed under new drug applications.

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Today's meeting will focus on an issue raised in a citizen petition submitted by Robert Seidman on behalf of Blue Cross of California. The petition was dated July 21, 1998. There have been subsequent amendments by the petitioner to this petition. The most recent amendment by the petitioner was submitted in October of 2000.

The petition requests that the agency convert the five prescription antihistamine-containing drug products listed here to OTC marketing.

[Slide]

I would like to address the areas that we hope will be the focus of discussion and which will be the focus of the presentation by the FDA. The first involves the OTC marketing of antihistamines as OTC drug products. Cazemiro Martin, from the Division of Over-the-Counter Drug Products, will provide an overview of antihistamines in the OTC drug review and how this category of drug products has been generally recognized as safe and effective

under its conditions of use.

The second is the safety profile of these products. Robert Meyer, from the Division of Pulmonary Drug Products, will present the FDA review and the safety of these procedures.

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There are four areas that the agency hopes will not become the focus of discussion by the committee. This, however, does not preclude any of the presenters from raising these issues in their presentations. The chair of this advisory committee will have the discretion to limit discussion of these issues by the committee.

The agency acknowledges that all the products have data in their NDAs to support efficacy. So, there is no need to go into detailed presentation or discussion of efficacy of these products.

Secondly, there is no need to discuss the legal authority of FDA to initiate a prescription to OTC switch. We are bringing this issue before the committee for their scientific expertise and not for their legal expertise.

Third, a switch from Rx to OTC status will not impact on any existing patents and exclusivity

remaining for these products. Consequently, there is no need to discuss this.

Lastly, with regard to the issue of cost of therapy and health insurer reimbursement, in making decisions on the approval of drug products for prescription or OTC marketing drug cost or reimbursement by health insurers are not factors in the agency's decisions. The agency does not have the regulatory authority to control the cost or health insurer reimbursement of drug products. The agency will base any decision on the merits of the scientific data for the individual drug products and will proceed under the mechanisms permitted by the regulations. Clearly, both the petitioner and the drug manufacturer control cost and reimbursement, and both have a secondary gain in favoring one outcome over the other.

[Slide]

Finally, the suitability of OTC marketing of Claritin, Allegra and Zyrtec should be based on their individual merits. The committee should consider them individually and not necessarily as a group. Secondly, relative comparisons of safety and efficacy to the currently marketed OTC antihistamines are not necessary.

I would just like to make one additional comment. Under the conditions of use the currently marketed OTC antihistamine products have been classified as generally recognized as safe and effective in the OTC antihistamine monograph, or they are marketed under approved new drug applications. In their petition, the Blue Cross of California has characterized the currently marketed antihistamines as dangerous but they have not provided data to support this characterization.

With that, I conclude my introduction and the agency looks forward to the discussion and recommendations of the committee.

DR. BRASS: Thank you very much, Dr. Ganley. At this time, I would like to turn the podium over to Dr. Seidman, from WellPoint Health Networks, to present the citizen's petition.

Blue Cross Petition

DR. SEIDMAN: Good morning, everyone.

[Slide]

I am honored and humbled to be here. In support of our petition this morning, I have Dr. Robert Crocker, who is Senior Vice President of Clinical Affairs for WellPoint Health Networks, and Dr. Mike Nichol and Dr. Jack Kern from the

University of Southern California School of Pharmacy.

[Slide]

Why am I here today? That is an incredible question. I wrote a letter; I am here today to ask the advisory panel to do something that is in the best interest of the American people. I am asking that you make a recommendation to the Food and Drug Administration to convert Claritin, Allegra and Zyrtec from prescription to over-the-counter status.

[Slide]

We filed our petition because we believe that Claritin, Allegra and Zyrtec lack any significant criteria that would require the Food and Drug Administration to maintain these drugs as prescription drugs. You can see the criteria that we filed this under. We believe that the Food and Drug Administration's jurisdiction in this area is clear.

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This has been a long and what I hope to be a productive journey. We have a unique opportunity today to obtain input from this country's experts on these drugs and get a decision on this important

issue.

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It is my hope that when all is said and done today the advisory committee will make a recommendation to the Food and Drug Administration to convert these incredibly safe and effective drugs to over-the-counter status.

[Slide]

Why did we submit this petition? This week it feels as if everyone on the planet has been asking me this question. Americans are seeking greater oversight over their health care. The over-the-counter status of these drugs will be more convenient for allergy sufferers. Allergy sufferers know how to use antihistamines, and precedent has already been set that antihistamines can be used effectively in the over-the-counter market. These drugs are safer than the over-the-counter antihistamines that are available today.

[Slide]

I have only one slide on pharmacy costs and I will be brief. The current increases in prescription drug costs are unaffordable and unsustainable. There are forty million Americans

who lack any health insurance. There are twenty-five million senior citizens who have no prescription drug coverage. Maintaining Claritin, Allegra and Zyrtec as prescription drugs does not protect the public health and is a major burden on the healthcare system, both public and private.

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Why are these drugs prescription? The presumption under Durham-Humphrey is that all drugs are over-the-counter unless professional guidance is required. There is no credible clinical reason for Claritin, Allegra and Zyrtec to be maintained as prescription drugs. If the Commissioner believes that the prescription drug status for these drugs is not necessary to protect the public health they should be available over-the-counter.

[Slide]

We believe that the second-generation antihistamines meet the criteria for an OTC switch. The questions that we need to ask are can the condition be adequately self-diagnosed? Can the condition be successfully self-treated -- all of this in an over-the-counter environment? Is the self-treatment product safe and effective for consumer use and conditions of actual use?

We know, because of the precedent of many over-the-counter antihistamines being available today, that patients can readily diagnose their condition; that patients can successfully self-treat; that patients can use these safely in an over-the-counter environment.

These drugs are available over-the-counter in many countries, and we have brought along a visual aid to show the over-the-counter packaging that is available. Claritin has been available over-the-counter in Canada for twelve years with an exemplary safety record. Using the FDA's own criteria, these drugs should be truly over-the-counter, not the virtual over-the-counter drugs that they are today.

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The forty million allergy sufferers in our country deserve ready and easy access to these safer drugs. The majority of allergy sufferers can recognize their symptoms. These drugs have less side effects than the current OTC drugs that are available today. They have side effects similar to a sugar pill.

I would like to now introduce Dr. Jack Kern, who will summarize the findings of an

evidence-based report comparing the safety and efficacy of first and second-generation antihistamines. He will be followed by Dr. Mike Nichol, who will review data on his quality adjusted life year study. The evidence-based study was funded by WellPoint Health Networks. The quality study was an independent venture of Dr. Mike Nichol. At the conclusion of their comments I will summarize. Thank you.

Comments by Jack Kern, Pharm.D.

DR. KERN: We were involved with this evidence-based project and, like all the evidence-based projects I have been involved with, it is an interesting approach to evaluating the literature to come up with a policy. We put together a team involving a research librarian and we identified approximately 289 titles that are involved with randomized, controlled studies of the first-generation and second-generation antihistamines. We screened these titles looking primarily for the studies having to do with the treatment of seasonal allergic rhinitis and perennial allergic rhinitis involved with drugs first generation and second generation, first-generation drugs being the diphenhydramine

and chlorpheniramine; the second-generation drugs being the fexofenadine, loratadine and cetirizine.

Of these studies, we reduced it down to 95, photo copied the articles, went to through them in a considerable amount of detail, and then we finally settled on 36 of the studies for our evidence-based report. These 36 randomized, controlled studies made up the basis for our meta-analysis.

Of interest, these populations that we focused on also reflect the OTC population. This is the primary indication of seasonal allergic rhinitis and perennial allergic rhinitis. We had several reviewers so it wasn't done just by one person screening these particular articles, and these references serves as the basis for our evidence tables.

One of the most important components of the evidence tables are the safety factors that have an impact on the outcome for the use of these particular drugs, and these significant factors have to do with the source of the antigens -- is it natural, environmental; having to do with pollen counts; having to do with the pollen source; having to do with the symptom scores, what kind of a

scoring system was used to evaluate the outcomes for these studies, whether they involved nasal congestion; and the duration of the observational period of time, was it one day, five days, or was it over a period of forty days?

The evaluator for the outcome was importantly screened for whether it was evaluated by the patient, by the physician or a combination of both, and also whether there was a period of lead-in time to evaluate whether patients actually had allergic rhinitis.

Based upon these findings in the evidence tables, we built our shrinkage plots, and this was in conjunction with a statistician. Then, after development of the shrinkage plots we developed our conclusions, had discussions and tried to understand why various studies had different outcomes. There is quite a bit of variance in this particular disease state so you would expect to see that all the studies wouldn't necessarily line up in terms of one number for efficacy.

[Slide]

Having to do with the efficacy of these studies, what we wanted to do was we wanted to take a look at the 36 studies and then begin to boil

them down one step further as to which studies we were going to pool together. We looked at the dose. The dose of the studies had to be the same. All of the studies had to be blinded because the nature of the outcome evaluation for seasonal allergic rhinitis is subjective, that is the primary endpoint. Then, the scoring system had to be the same. There are several different scoring systems. We wanted the system and the point scores that were given to be similar between these. And, out of the 36 we identified 28 studies that were compatible to be able to combine the studies for the different drugs.

For example, for loratadine one of the studies had to do with perennial allergic rhinitis; the remaining studies were of seasonal allergic rhinitis. This may sound like you are mixing apples and oranges but, in fact, in the general public this is what we were trying to mimic, the use of the drug in the society where you may expect the OTC population. They wouldn't all be just one particular group; they would be varied. This would also create a larger variance in our overall evidence report and not try minimize it to just get the maximum number but try to get a more realistic

assessment. The duration within the loratadine studies varied quite a bit from just one dose over a five-hour period in an experimental chamber where the patients were exposed to a high dose of pollens as compared to the remaining studies which were in the natural environment.

In this disease of seasonal allergic rhinitis there are typically five different antigens that are associated with allergic rhinitis, and these have to do with pollens, mites; having to do with molds, animals and having to do also with insects. Patient sensitivity to these different pollens is quite considerable so there is a tremendous amount of variation in how a group of patients will respond to these drugs. Also, over the course of time patients' sensitivities to these particular antigens change. So, there is a lot of variance in terms of a given response.

The outcome we looked at in this case had to do with global efficacy, and we considered a positive response if patients were asymptomatic or markedly symptomatic [sic] so that they would be able to function normally in their daily life.

As we see in these studies with cetirizine, we identified seven studies and the

overall effect size was a reduction of the symptomatology by 24 percent. With loratadine the reduction was 21 percent; and with cetirizine in children there was a similar reduction of 26 percent. Cetirizine compared to loratadine -- we had a head-to-head evaluation between these two and it appears that perhaps cetirizine may be a bit more effective than loratadine.

Of significance was taking a look at the comparison between first-generation and second-generation antihistamines, and this was between chlorpheniramine and terfenadine. Terfenadine, as of 1998, was removed from the market in the United States but it is a second-generation antihistamine and it is a situation where we had a head-to-head evaluation of the efficacy between these two.

Of interest, in an evidence-based report you are not allowed to generate data. You are allowed to evaluate what data exists. That was the reason why we selected those particular two, showing that, in fact, second-generation antihistamines are equivalent in terms of efficacy to the first generation.

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Having to do with the side effects of the first-generation and second-generation antihistamines, the side effect issue is the main difference between these two particular drug products, and we identified 29 of the studies of the 36 that gave us information as to whether the patients complained of these particular side effects or not. We see with the chlorpheniramine that the incidence of sedation was approximately 17 percent, and then in adults and children with cetirizine it was the same, about a third of what it was with the chlorpheniramine of 5-6 percent. With loratadine, of 11 studies the overall incidence was zero. It was not any different than compared to placebo. With fexofenadine, there were 5 studies that we identified with fexofenadine and 4 of them did not give us any report on sedation or did not report that sedation was a complaint that the patients had while they were receiving that particular drug.

So, we see once again that based upon this significant distinction between these particular groups of drugs that the sedation profile had a much higher incidence in the first-generation than the second-generation antihistamines.

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In conclusion, the quality of these studies is high. They are randomized, controlled studies. They were all blinded. They had to be in order to evaluate the particular outcomes for these studies. The population is similar to what would be seen in the OTC population. And, we see a similar effect between the first generation and second generation of approximately one in four, one in five patients having a very good response to these particular drugs.

You may also ask, well, what about the other 80 percent, 75 percent -- yes, there is considerable amount of variation in terms of response to these participant diseases and this begins to set up a situation. In 1998 there was a major joint task force of three of the allergic societies in the United States. They came together to put together a consensus report on the diagnosis of treatment of rhinitis, and their general consensus was that the most appropriate use of an consultation with an allergist was in patients that failed first-line therapy for the treatment of allergic rhinitis, which is typically having to do with antihistamines.

So, their conclusion in terms of the issue of efficacy is that the first-generation and second-generation antihistamines are equivalent. The difference between the two with regard to sedation -- the idea of sedation is significant but where it really begins to be important is having to do with performance.

The Federal Aviation Administration has come to the conclusion that the second-generation antihistamines are safe and effective for pilots to use while flying if they do not experience any symptoms of sedation while receiving the second-generation antihistamines, whereas with the first-generation antihistamines it is not appropriate for pilots to use these drugs while on duty.

There have been studies evaluating the use of these two groups of drugs with regard to driving, and the conclusion is that the first-generation antihistamines produce a sedative performance compromising the drivers, equivalent to 0.05, 0.08 equivalence with ethanol, and that the impairment of driving by the second-generation antihistamines is minimal to none.

Having to do with the cardiovascular

toxicity of these particular products, there have been a major epidemiological studies that have looked at these particular drugs and have found that the first-generation antihistamines are associated with a significant incidence of serious cardiac abnormalities, arrhythmias, as opposed to the second generation which have not. This is where the incidence with terfenadine became of interest in that terfenadine in combination with drugs that inhibit its metabolism and that subgroup the incidence of serious cardiac abnormalities was identified and, therefore, the drug was removed.

With regard to loratadine, the drug has multiple sites of elimination so this particular drug interaction is not as significant. Cetirizine is primarily eliminated renally, compromising its ability to be metabolized and eliminated and does not have a significant effect on cardiac toxicity.

Fexofenadine, and it is the active metabolite of terfenadine, has been given in very high doses, ten times above the usual and ordinary dose, and cardiac dysrhythmias have not been identified with that particular drug.

So, at this time the evidence is quite supportive of a conclusion that the two groups of

drugs are equivalent from an efficacy point of view, and that the second benzodiazepine antihistamines are safer and, therefore, should be available for people to use for treatment of their seasonal allergic rhinitis, perennial allergic rhinitis. With that I conclude.

Comments by Michael Nichol, Ph.D.

DR. NICHOL: Thank you very much, Jack. It is a pleasure to be here this morning and I would like to just point out a couple of things prior to exploring some of the issues related to our cost-effectiveness model.

First of all, as Rob indicated, this research was internally funded at the University of Southern California. This has not been supported by any insurers nor any pharmaceutical company. The second thing is that this model has not been peer reviewed at this time. So, consequently, I look at this as an opportunity for us to get some comments back from you as well as others prior to going through the peer review process and publication process.

[Slide]

So, why are we motivated to look at the cost effectiveness associated with an Rx-OTC

switch? Obviously, as Prof. Kern has already discussed, the meta-analysis that was recently completed points out that there are some very important differences with regard to some of the sedation side effects and, consequently, Patrick Sullivan, a doctoral candidate in our program, and I embarked on the idea of looking at what the cost effectiveness may be with regard to that sedation.

So, the study purpose that we had was to identify the assumptions of a cost-effectiveness model and also vary some of those assumptions to see whether or not there are some key issues that we need to resolve. The model that we have is a decision analytic model. The perspective is societal to the extent that we can within the data that are available. The period of analysis that we have is just one year. Our cohort is the adult population in the United States, actually the driving population in the United States. And, the comparison, the specific comparison that we made is the prescription loratadine versus over-the-counter loratadine, primarily because, as Dr. Kern indicated, the studies that are available make direct comparisons between some of the first-generation antihistamines and loratadine.

The impact that we modeled was on motor vehicle accidents -- the effects of sedation on motor vehicle accidents. Redelmeir and Weinstein, in a piece that was done not long ago in Medical Decision-Making, looked at the effect of cell phone utilization on motor vehicle accidents and had a very nice model that we could adapt with regard to sedation. The output in this particular model is cost per quality-adjusted life year.

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The incremental cost-effectiveness ratio for this particular model shows that there is a cost saving to society of approximately 62,000 dollars per quality-adjusted life year. Those of you that have looked at cost-effectiveness analyses before recognize that this is a fairly remarkable finding given the fact that in the United States we generally adopt innovations that cost society about 50,000 dollars per quality-adjusted life year.

Well, what is the source of the savings that accrue from this particular model? When we looked at the base case, what we did was we used, as I indicated, a model that was developed by Redelmeir and Weinstein with regard to the effects of collisions. In terms of the relative risk of

sedation, there are four different studies that point out, as Prof. Kern indicated, that the effect of sedation is roughly similar to being legally intoxicated behind the wheel.

In terms of the risk of fatality and the risk of injury, that was deduced from material that was provided by the National Highway Traffic Safety Administration. With regard to the percent of patients that are being treated by physicians, that was derived from the literature, an article by Malone in Allergy and Clinical Immunology. Then, we made two very important assumptions, I think. They may not be as important as you might think from the beginning when we started to look at this model, and that is that we assumed that given there was an M.D. visit, the proportion of the market that would be given to the second-generation antihistamines, we estimated that the base case that that would be 80 percent, and then what would happen once these medications might be transitioned to an OTC market we were assuming a 50 percent market share on that.

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We find that there is a dominating solution, and in this case with the cost-savings

effects there is clearly a dominating solution. We may conclude, consequently, that it is not necessary to do any additional analyses. However, in this case it may be very useful for us to look at what some of the key issues are that may drive this type of a decision.

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In this case we applied a sensitivity analysis and looked at the percent drop in the non-sedating price after an OTC conversion. Our base case anticipated that the price would actually drop by about 66 percent. Again, this was modeled off literature on the H-2s, the GI-related medications, because after they went over-the-counter there was a drop in price of about 66 percent. So, we can obviously say, well, maybe it is not going to drop that severely and, at this point, what this shows is that, using our base case scenario, if the prices only drop 27.5 percent this would still be a cost-effective innovation with regard to American society.

Note also here that we are assuming that the OTC present first-generation antihistamines are also going to be dropping 66 percent. If, in fact, those prices do not change what happens is that it

turns out that it is still a much more cost-effective solution. That is, the prices for the second generation, as they convert to OTC, could drop as little as 10 percent and it would still be cost effective.

One of the other key issues is the percentage of the population with allergic rhinitis that is being treated by M.D.s. As you can see with this particular slide, our base case was 12 percent. This was based on the literature that we had available at the time. As you can see, if we increase that proportion, that is, if we decide that, in fact, maybe 25 percent of the people are being treated with allergic rhinitis you can see that it becomes even more cost effective as we move through this particular analysis.

[Slide]

So, our preliminary analysis indicates that in this case the conversion from Rx to OTC would actually be cost saving to society. One of the things that I think is very important for us to realize is that we are anticipating this analysis is what we would call a zero-sum gain. We are not anticipating that the market is going to expand. We clearly need to do some work with regard to

modeling the effects on both price and also the elasticity of demand, and that is some of the work that we will be doing subsequent to this.

Another issue that was raised in a briefing paper by Schering Plough was the impact that this might have in terms of the inappropriate use by consumers. As we indicate here, there are a number of issues that you may need to consider when you try to model that inappropriate use. However, with this model one thing that would can do is look at how bad would the inappropriate use have to be for this type of conversion to not be cost effective.

In our modeling, it appears to us that in this case 100 percent of the patients that are being presently treated with prescription medications could incur an additional 150 dollars on average in a year and the conversion would still be cost effective. That means that we are talking about an additional two or three offsets for 100 percent of that prescription population. On the other hand, 13 percent of that population could incur up to 2500 dollars in hospitalization costs and this innovation would still be cost effective.

So, in conclusion, it appears to us that

there are some significant issues with regard to the cost effectiveness associated with these medications. The superior safety profile and the non-sedation effects are very important with regard to cost-effectiveness analysis. And, I appreciate your attention.

Comments by Robert Seidman, Pharm.D.

DR. SEIDMAN: Thank you, Dr. Kern and Dr. Nichol for presenting the science.

[Slide]

Briefly, our petition is being portrayed as being unprecedented but in reality it is not. In 1982 the Food and Drug Administration converted Alupent from prescription to over-the-counter status, and the FDA's authority in making these decisions is absolutely clear.

[Slide]

Let's talk a little bit about the public interest. These products meet all requirements for over-the-counter status. There is a long history of over-the-counter marketing of antihistamines in this country. These drugs are effective and safe. As we have heard, they have a low incidence of side effects and are equally effective. Switching these products to over-the-counter status will make safer

products accessible to the public. Converting the second-generation antihistamines to over-the-counter status is in the public's interest. Society deserves open and easy access to these incredibly safe and effective drugs.

[Slide]

When I was here last June I was asked for comments on prospective over-the-counter labeling for Claritin, Allegra and Zyrtec. Looking at some of the labeling that we have in the country today for over-the-counter antihistamines and stealing a little information from some of the Canadian labeling, we have some draft labeling that can easily fit on a box to help the 40 million allergy sufferers in our country to take greater control of their allergies.

I have also brought some samples that are velcro'd to the board. I encourage anyone in the room to please come and look at these. Please return them when you are done because they are not allowed to be sold in this country at this time. As you can see, the OTC labeling is safe and allergy sufferers will be able to understand and self-treat where appropriate.

[Slide]

This has been a long and I hope a productive journey. The questions asked today help firmly position Food and Drug Administration in the role that society expects, providing broad access to safe drugs. We would like the advisory committee today to vote and make a recommendation to the Food and Drug Administration to allow Claritin, Allegra and Zyrtec to be sold over-the-counter to benefit the allergy sufferers in our great nation. We also expect the pharmaceutical industry to abide by whatever decision is rendered by the Food and Drug Administration. This healthy debate has helped all Americans. Thank you very much.

Questions from the Committee to Blue Cross

DR. BRASS: Thank you. At this time, we have a period where the panel can ask questions of petitioner. Before we begin that, I ask the panel to remember the introduction presented by Dr. Ganley with respect to the scope of the questions, and that we will have subsequent presentations by two of the current manufacturers as well as the FDA providing more detail. Given that, if there are questions for the petitioner from the panel -- yes, Ralph?

DR. D'AGOSTINO: I understand what was said about the focus of the committee deliberations, but I would like to ask just a couple of questions in terms of the meta-analysis and then a couple of other questions.

The decision analysis has not been peer reviewed. Has the meta-analysis been peer reviewed?

DR. KERN: No, it has not been peer reviewed at this time.

DR. D'AGOSTINO: There is a large number of studies that were potential and then a small number of studies analyzed. Let me just go on. I am a great advocate of antihistamines, at least the first generation, being put in OTC medication packages for common colds and so forth. Is the notion of the second generation that they would, in terms of this replacement -- and, you know, what would be the level of first generation -- that they would take the place of first generation? I mean, I am interested in how the safety and the use of the actual second generation will play itself out with the OTC, and one possible use is that people will start taking it for their runny nose as they catch a cold.

The other is the drug interactions. I am not sure that we understand all the drug interactions that the second generation have and I just want to get a sense of what the petitioner is actually saying about those. Are we ready to just go straight OTC?

DR. KERN: I think that is an interesting issue as to whether the first generation should be dropped. I don't think so at this time for the reason, as I mentioned, that in the whole picture of this seasonal allergic rhinitis there is a lot variance in the population, and patients and people who are having a positive response to the first generation, I don't think they should be denied access to that drug. The typical recommendation in the allergic community is the allergist is to start with a second-generation antihistamine. In the situation where it appears that it may be of benefit to move to first, there may be those occasions to do that and that would probably be the exception by far. The topical use of inhaled steroids is probably the most effective drug that you can use.

So, there are several options that can be used, but in terms of your question about dropping

at this point, probably not because there are people who are responding to this drug. The other side that does make me feel uncomfortable about the idea of not dropping it is that many people that feel that they don't have any symptoms of sedation, when they are tested in terms of their driving performance, they are compromised. So, there needs to be some debate about that as to what the consequences are of individuals that feel that they are not having any adverse effect but, in fact, their driving ability is being impaired. So, this needs to be discussed further.

DR. SEIDMAN: I would like to comment briefly about the meta-analysis being peer reviewed. We now have three analyses that appear to justify the incredible safety and equal effectiveness of these agents. There is the meta-analysis that we contracted with the University of Southern California; there is the Food and Drug Administration's own analysis of the world literature on these agents; and most recently, there is a MEDLINE search that has been performed by the American Pharmaceutical Association that will be published in this month's journal. All three studies conclusively state that

these drugs are safer and equally effective to the first-generation antihistamines.

DR. BRASS: Thank you. I just want to follow-up to reiterate a couple of points, and the FDA can correct me if I misspeak. First, the citizen's petition does not address at all the status of what has been termed the first-generation antihistamines and, therefore, that is not an issue.

As you are well aware because you participated, that previous panel and the FDA have extensively reviewed the OTC status of those first generation in a very comprehensive and deliberative process and determined, based on data, that the indication was an appropriate OTC indication and that the first-generation agents were generally recognized as safe and effective. Unless new data is presented, I do not think the status of the first-generation agents can be directly addressed.

DR. D'AGOSTINO: The other part of my question was are we convinced, or is the petitioner convinced that drug interactions have been handled with these safety databases that do exist in our experience? Is it long enough to have that information?

DR. SEIDMAN: I would defer to the FDA's own information. These drugs are over-the-counter in 17 countries. There is 12 years of experience in Canada -- exemplary safety record compared to the first-generation agents.

I apologize for going back to my financial slide but the healthcare system experienced over a 600 percent increase in antihistamine costs between 1993 and 1998, and that was secondary to the wide acceptance of these agents being prescribed more than any other antihistamines that were used previously in first generation. I believe that the science on the safety of these products is such that there is no doubt regarding their safety.

DR. BRASS: Dr. Vollmer?

DR. VOLLMER: I just have a comment regarding the cost analysis. One, and I think this is going to be a recurrent theme throughout the day, I hear from the introductory comments and from materials in our packets that many of the issues being presented to us are really not on the table for us to be considering and, yet, we are going to see a lot of these issues trundled out today. So, it is helpful to keep remembering that.

Even ignoring that, I must admit that from

my own perspective it is very difficult. Not only is the cost analysis not peer reviewed but I don't have any details. Until today all I had was a one-page summary of it so I can't even get my own evaluation of it to determine whether there are any potential flaws or limitations to it. So, it is very difficult to assign much credibility to that without any information above and beyond what we have seen.

DR. BRASS: Yes, Dr. Niederman?

DR. NIEDERMAN: I have a question but first a comment about the peer review. I think if you are going to be placing as much value on these two analyses as you are, it is unfortunate that you haven't gone through the peer review process. I don't understand, given the time lines here, why you haven't done that. I think, as Dr. Vollmer said, there is just not enough data in the cost analysis to really make any kind of logical conclusion and I think for something this important you should have either not presented this or should have presented it for peer review before you presented.

But having said that, my two questions relate to the lower but still measured sedation

potential of these second-generation agents. There is some sedation and my question relates to your model. First of all, I assume that you presumed there was no sedation and, therefore, no accidents associated with the second-generation agents, and I am sure that that is incorrect given the data that we have seen. And, that would be just one example of the problems with this model.

Along those lines, with the proposed labeling that Dr. Seidman showed there is no warning to consumers at all about sedation potential, and I wonder whether you feel comfortable with that. Even though this is less sedating than the first-generation agents, should there be a warning if these were to be over-the-counter because there is at least some population that gets a sedation effect?

DR. NICHOL: Let me comment about the first two issues that you raised. With regard to the peer review status on the cost analysis, we actually completed the meta-analysis approximately two months ago and, consequently, as you well know, the review process takes a considerable amount of time. The reason that it was presented today is to illustrate, using an existing model that had been

reviewed, the impact on the use of cellular phones on automobile accidents -- modeling in a very similar way to showing how important sedation may be only with regard to motor vehicle accidents.

I think our concluding slide which pointed out that there are a number of other areas that we need to explore illustrates that there may be also some other effects that will be very important to society, such as the impact on workplace productivity.

With respect to the second point that you had about the assumption regarding sedation effects for the second-generation antihistamines, you are correct. We assumed that there would be no sedation effects. Having said that though, it is also important to realize that our base case analysis assumed that the first-generation antihistamines, instead of having a 17 percent effect which was presented in Dr. Kern's meta-analysis, we assumed about an 8.5 percent sedation effect. So, we have the effect in terms of the first-generation products. Actually, we have done some sensitivity analysis with regard to the sedation effects on the second-generation antihistamines and it would not produce a profound

impact on the bottom line given the analysis we have done so far.

DR. BRASS: Dr. Wood?

DR. SEIDMAN: I would like to just comment before we go on to another question. The FDA guidelines for the conversion from Rx to OTC are clear -- can a patient in the over-the-counter environment self-diagnose an allergy? And, the labeling that is in place today on the plethora of OTC antihistamines clearly documents that patients can self-diagnose allergies.

Second, can the patient understand the drug regimen in the OTC marketplace? With the incredible direct-to-consumer advertising on these drugs, taking a tablet once a day, there is no question the patients can understand these drug regimens in an over-the-counter environment.

Third, are there any side effects from these drugs that would preclude their being sold in an over-the-counter environment? Again, I apologize. I go back to the direct-to-consumer advertisement that has been approved by the Food and Drug Administration that says that these drugs have minimal side effects or side effects similar to a sugar pill.

The FDA has already de facto decided that these drugs are safer and equally effective to the over-the-counter antihistamines. Why then do we deny ready and easy access to these safer agents to the forty million allergy sufferers in our country? It just doesn't make any sense.

DR. NIEDERMAN: I didn't hear an answer to the question about your label. You don't want to put any mention of sedation in the label? Do you stick with that?

DR. SEIDMAN: We defer the OTC labeling to the Food and Drug Administration. Our proxy labeling was for loratadine which has minimal to zero side effects in terms of sedation. At least, I haven't received a letter from the agency instructing me to develop the OTC labeling. The labeling was an example to show that it is easy to label Claritin, Allegra and Zyrtec for over-the-counter status.

DR. WOOD: One of the issues we have to debate today I guess is whether patients can self-diagnose and use these drugs safely. Though we are not supposed to revisit the first-generation antihistamines, it does seem to me that it would be impossible to ignore the fact that first-generation

antihistamines have been widely promoted and vigorously promoted by many of the same players who are now telling us that these same patients can't diagnose that.

So, I would like to hear if there is evidence that people have used first-generation antihistamines inappropriately, and was that figured into the models that you used to calculate the financial loss to patients and to society.

DR. NICHOL: No, we didn't do that. There is no literature actually available that looks at the inappropriate use of the first-generation antihistamines.

DR. BRASS: Dr. Apter?

DR. APTER: I too am unaware of any information about inappropriate use but I can tell you, as a clinician, I see frequent inappropriate use of antihistamines by my patients, and also physicians referring patients may prescribe antihistamines when, after a full evaluation, there are no allergies and antihistamines would not be appropriate. So, I think the question before the committee and for those of you presenting today is if antihistamines second generation are taken inappropriately, is it safe.

DR. KERN: Well, I think this question of self-diagnosis begins to run into the next question, what if -- if the patient does take a second-generation antihistamine inappropriately? And, I think that is the important distinction as to what we are talking about. The same would apply with the first generation inappropriately, and the difference has to do with the side effects. So, it is not a huge leap but it is a logical leap that if you were to take either one of those drugs inappropriately, which one would have the greatest consequences, negative consequences to the patient. By and large, the way that people are looking at the benefit to risk ratio, the second generation have a higher benefit to risk ratio than the first, and I think that would apply to that same scenario in terms of people using the drug inappropriately.

DR. BRASS: Dr. Krenzelok?

DR. KRENZELOK: Safety is obviously a major issue with the antihistamines. You have used the Canadian information data from adverse drug reporting and so on to make your case. In California you have four poison centers that generate about a quarter of a million poison information reports a year. The American

Association of Poison Control Centers Toxic Exposure Surveillance system generates about 2.2 million exposures per year. So, there is an incredible database for you to potentially mine to determine whether or not there are safety concerns.

I was just looking at the most recent report from the AAPCC, and in '99 there were about 52,000 antihistamine exposures reported. About a third of those actually ended up being treated in a healthcare facility, which is an inordinately high number. So with that, my question is have you looked at these databases as another source of safety information to determine the safety of all three agents?

DR. NICHOL: Actually, I have not looked at that information in terms of the utilization, but it sounds like from the standpoint of the utilization that you just discussed, the sensitivity analysis that I referred to at the end of my presentation is probably very relevant, that we are looking at the possibility that there is some substantial inappropriate use that may result in additional utilization of the healthcare system. The question is whether or not, from my standpoint, there is a tradeoff with regard to additional

access. At this stage of the game, without any further analysis, it looked to me from that standpoint like the tradeoff is at least a wash.

DR. BRASS: Dr. Neill?

DR. NEILL: I am curious to know whether there are any actual use studies in the U.S. or in any of the currently OTC marketed countries that address any potential risks accruing by membership in a subpopulation. I have read the meta-analysis that suggests that there are no risks and that there are no subpopulations, either by virtue of having metabolized the drugs, co-morbid conditions, propensity to sedation -- that those subpopulations don't exist. Without reviewing the individual studies, I can't get a sense for whether or not that has been looked at specifically in an actual use study.

DR. KERN: This brings up the same question having to do with this risk and looking at an epidemiological point of view. I think the incidence of these types of effects, like the cardiovascular, are very small but they can be significant. So, what it requires is clinicians, as we have many in this particular audience. If you make any kind of an observation where this may

be a possibility then I think it sets itself up to look into this type of database. So, what it is implying and in terms of what has actually happened is that these particular connections between very unusual type of events have not been observed and have not been put together.

With regard to that database that was looked at for the cardiovascular, that had to do with Medicaid patients over a four-state population, and they did a very good job of identifying the incidence of the serious cardiovascular consequences. So, the point I am getting at is that if there are observations of potential links these databases are available. To go through a witch hunt to take these databases and just try to find anything that may come up as being a potential has never been found to be an effective way of using science and using databases in order to try to find out something that is meaningful.

So, you have to have the pathophysiological link, like we talked about the drug interactions with terfenadine. This begins to make sense. The drug levels go high and you can see the cardiovascular toxicities. It makes sense from a physiological-pathological point of view.

So, this is what needs to be done. These databases are available, if there is a particular observation that would link somebody, to look in that direction.

DR. BRASS: I just have to point out that terfenadine was identified from a clinical signal before the pathophysiology was identified. Dr. Clapp?

DR. SEIDMAN: If I could just make one comment before we continue? We are having some excellent discussion I think on how much data is enough, and I think we need to talk about that a little bit. There is a wealth of information on the safety and efficacy of these drugs. The direct-to-consumer advertising on these drugs is clear that these drugs are safe and equally effective. Are we going to wait until December of 2002 for Claritin? Are we going to wait until 2007 for Zyrtec? When will we make these drugs available to the American public?

DR. BRASS: You have made that point. Please try to respond to questions only. Dr. Clapp?

DR. CLAPP: Currently, all three second-generation antihistamines are marketed and

indicated for chronic idiopathic urticaria. I am curious as to how the Blue Cross petitioners plan, suggest or propose prescription status for this indication. Do they propose a nonprescription status for the use in allergy, seasonal allergic rhinitis, and a prescription status for chronic idiopathic urticaria?

DR. SEIDMAN: When we filed the petition we felt that making these drugs more broadly accessible was in the public's best interest. We will defer to the Food and Drug Administration for specific labeling on those indications.

DR. CLAPP: So, your packaging for use in allergy would have nothing to do for an indication for urticaria? You wouldn't mention that in your proposal? You wouldn't suggest that the patient population have access to these drugs for the purpose of urticaria?

DR. SEIDMAN: Again, I would defer to the Food and Drug Administration for the specific labeling for the over-the-counter versions of these drugs.

DR. BRASS: Dr. Fink?

DR. FINK: Yes, since you have made public access a major part of your petition, do you have

comparative data about use per 10,000 individuals in those countries where the drug is OTC versus the United States where it is prescription? That is, is there actually increased use per population unit in the over-the-counter countries?

DR. SEIDMAN: We have no data on that.

DR. SACHS: Going back to the meta-analysis, and since we don't have a lot of detail it is hard to tell, but apparently there were about 200 or so studies you reviewed and only 30 were included. I am curious about why some of those others were rejected, only because sometimes that is where you lose some data that is important. I don't know if the FDA had also looked at that, you know, if we can accept this as the safety.

DR. KERN: That is always an important part of the analysis, the rejection criterion. The studies that we were looking at, once again, were focusing in on adults, children, seasonal, perennial allergies, and they were not focusing -- like the question that was brought up having to do with another indication -- to be honest with you, from my point of view, we didn't look at that. I don't really have any comment. If that was to be brought up in terms of whether this is safe and

appropriate for that group, I think we would have to focus in on that particular group. We eliminated urticaria from our focus because we wanted to focus in on something that we felt was large enough but we weren't able to focus in on every particular indication that these drugs are used for. Some of the studies that were eliminated were based upon that indication. Other studies had to do with the chemical reaction. People were testing to see what the actual chemical reactions were to these individuals and we eliminated those because those particular studies used various different types of measuring devices and we wanted to focus in on the symptomatology and the utilization of these drugs that would probably be the most appropriate for the over-the-counter population.

DR. BARAINUK: I have three quick questions. You have done a lot of work, it sounds like, on motor vehicle accidents. What is the relative risk of the first- versus second-generation antihistamines for motor vehicle accidents? Do you have an odds ratio?

DR. NICHOL: Yes, we do. There are four studies that have been done on that and their

estimates range from 5 to 16 relative risk. Our base case analysis used 4 as the relative risk.

DR. BRASS: Just for my clarification, those are studies comparing the two generations of antihistamines?

DR. NICHOL: Those are studies demonstrating the effect of first-generation antihistamines, and it gets back to that issue about whether or not we assumed that there was no sedation associated with the second-generation antihistamines.

DR. BARAINUK: So, do you have a number for the second-generation antihistamines?

DR. NICHOL: No, there isn't a number for the second-generation antihistamines.

DR. BARAINUK: And, for comparison what is the relative risk for alcohol?

DR. NICHOL: The relative risk for alcohol is roughly comparable as I understand it.

DR. BARAINUK: Do you have data or do you just assume?

DR. NICHOL: No, we are using the same estimating procedure that Redelmeir and Weinstein did in the piece that they had published in Medical Decision Making a year ago.

DR. BARAINUK: The second question I have is on the common cold. The first-generation antihistamines have a beneficial role there because they have anticholinergic properties. The second-generation drugs were designed because they do not have those properties. Would you, therefore, in your packaging contraindicate the use of these drugs for the common cold? Many patients make mistakes. They don't understand when they have a cold; when they have allergic rhinitis.

DR. KERN: In terms of the consequences, I would say for the common cold, no, it is not the indication. For having to do with the idea that if you have an allergic reaction that the patient is experiencing, that is the indication for the first or second-generation antihistamines, not having to do with the indication for the common cold.

DR. BARAINUK: It raises the question of self-diagnosis though and the appropriate use of the drug.

DR. KERN: Yes, and this is what I think is the real question in terms of the self-diagnosis, and that is what is the overall toxicity associated with the second generation compared to the first because what you are bringing

up also applies to the first generation. So, you have a relative issue that is going on. If somebody misdiagnoses, what is the consequence for that particular individual if we compare looking at these two different groups of drugs? It is becoming apparent that there is less risk to the individual if they misdiagnose and they are taking the second generation compared to the first.

DR. BARAINUK: Finally, what is your stand on pregnancy?

DR. KERN: Well, pregnancy -- to be honest with you, we looked at -- I don't know; I don't know.

DR. BARAINUK: This is not a trivial point. The current practice parameters recommend diphenhydramine chlorpheniramine first-generation antihistamines. The second generation are category B, but they are not generally written into the practice parameters as being indicated.

DR. KERN: I think this is correct.

DR. BARAINUK: Would many pregnant women be using these drugs, and what would be their risk?

DR. KERN: In terms of the studies that we looked at, to be honest with you, we did not focus in on pregnancy as being a primary co-condition

that these patients have. So, I really don't know exactly what the data is having to do with the use in pregnancy.

DR. BARAINUK: So, you would contraindicate the use in pregnancy?

DR. KERN: What I would do, if this is an issue that is critical, is take a look at that particular issue; that is what I would like to do. At this point we don't have any data in terms of the evidence to make that particular decision. We didn't put that into our particular mix.

DR. BARAINUK: You didn't look at it? And one final point, in general when drugs have been switched to OTC the doses have been cut in half. Is that so in general?

DR. BRASS: No, that is not necessarily true.

DR. BARAINUK: These would be available at the current doses?

DR. KERN: I would say yes. This is the evidence that we have that have studied these drugs. If you start reducing the dose substantially, cutting it in half, then we need to redo this particular type of investigation. I think we need to look at the data that we do have

and evaluate it as it is with the particular doses that have been studied, and not be tampering with that unless you are proposing that we redo all these particular studies.

DR. BRASS: There will be additional time for the panel to ask questions this afternoon. At this point, I would like to move on and turn the podium over to Dr. Nader, from Aventis, to give the first response to the petitioner.

Response to Petition by Aventis

DR. NADER: Thank you, Mr. Chairman. Ladies and gentlemen, good morning.

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We are here today to assess whether the prescription to OTC switch of the non-sedating antihistamines, as proposed by Blue Cross of California, would be in the best interest of patient safety and overall public health.

Aventis has given a lot of thought to this important question, focusing, at FDA request, on the safety perspective. We worked with our scientists but also consulted with medical opinion leaders, public health experts, as well as consumer groups. We also carefully reviewed the sequence of events that led to the withdrawal of Seldane from

the market. We finally analyzed the contentions of the Blue Cross petition and their motivation.

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We appreciate the opportunity to share our findings with the panel members and with the agency. Based on our analysis, we believe a switch of Allegra from a prescription status to OTC is premature. Allegra is still a relatively new product. We have not yet accumulated the experience and the data that would be essential to consider a switch and, therefore, caution and deliberation in our actions are necessary.

The switch of the non-sedating antihistamines to an OTC status would be, in our opinion, inappropriate, unnecessary and potentially adverse to the patient's safety. This process today is also unprecedented and, we believe, unwarranted.

Finally, shifting the diagnosis responsibility, the treatment accountability and the cost burden from providers and managed care to patients, as Blue Cross recommends, could have direct and indirect unintended patient safety and public health implications.

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Let me first address why we believe the switch of fexofenadine is premature. Fexofenadine is still relatively a new compound. Allegra 60 mg twice a day was first introduced less than five years ago. Allegra 180 mg once a day -- Allegra 60 mg tablets -- were introduced just about a year ago. Finally, Allegra 30 mg for pediatric use was introduced also just about a year ago. No one can argue that fexofenadine is safe when prescribed by a physician and used as labeled.

Although we are confident in the excellent safety profile of the drug, we are still at a relatively early phase of drug characterization. For example, fexofenadine is still in clinical development. We are actively pursuing clinical development work in asthma, in atopic dermatitis and additional pediatric development. In this last case, the FDA has mandated that the study protocols include a thorough assessment of unanticipated adverse reactions, particularly excitability, somnolence, fatigue and/or hyperkinesia. The FDA also asked us to run EKGs on all pediatric patients included in the trial.

We are also actively studying fexofenadine in a number of Phase IV safety and effectiveness

trials. We are also extensively monitoring the post-marketing experience with fexofenadine, including the evidence of adverse events. This information led us to make a number of labeling changes.

History provides all the more reasons why we should not rush to a judgment on a switch. During a painful period in our predecessor company's past we had begun to evaluate a switch of Seldane, another noon-sedating antihistamine. At the time neither the company nor the FDA believed there were any significant safety issues associated with the drug. However, Seldane was ultimately withdrawn from the U.S. market because of drug-drug interactions leading to serious cardiotoxicity when the drug was not used as labeled. We need to remember that at the time of withdrawal Seldane had been on the market for more than ten years and we had accumulated over 24 million patient years experience.

We do not refer to Seldane because of any comparative concerns with fexofenadine but, rather, to illustrate the importance of process; the importance of time on the market; and the importance of patient exposure. The

pharmacological properties of Seldane were also very well defined at that time. Yet, only time and the all-important post-marketing surveillance system associated with prescription drugs enabled the company and the FDA to identify and characterize a rare adverse event in a timely manner. Fortunately, once a drug is sold over-the-counter the quality and the quantity of adverse event reports declines to such an extent that they are no longer reliable. Our ability to continue building the post-marketing experience and the product knowledge will effectively end.

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We really do not comprehend the rush in this process. The Seldane experience, the recent withdrawals of PPA and astemizole from the market provide compelling testimony that a switch at this stage would be premature and that caution and an orderly process should guide our decisions. We have real concerns about this unprecedented process of forcing medications to over-the-counter status against the wishes of the manufacturers.

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Blue Cross, a party with no legal or regulatory oversight responsibility has requested

extraordinary action with respect to three distinct drug products. To further distinguish this case from the norm the three manufacturers oppose the switch, in part because of an unanswered potential safety and public health questions. Only once in the last 18 years has the FDA approved over-the-counter sales of a prescription drug without the support of the drug's maker. The FDA had, however, to switch the drug Alupent back to a prescription status shortly after it went OTC.

We also believe it is scientifically and medically incorrect to consider all the non-sedating antihistamines as one category. The non-sedating antihistamines are chemically and pharmacologically different in the way the drug is metabolized.

Blue Cross has brought what it suggests are, and I quote, OTC products in Canada. I would like to draw your attention to the fact that this is not correct. In fact, according to Canadian statutory requirements these drugs may only be sold as listed on Schedule 3. In Canada, the equivalent of the U.S. OTC status is the unscheduled status, and the non-sedating antihistamines are, in fact, listed on Schedule 3 in Canada. Schedule 3 means

that the drugs may only be sold under the supervision of a pharmacist as a learned intermediary who must be available, approachable and accessible to assist the patient in making an appropriate medication selection.

This Canadian experience is not comparable to the U.S. OTC environment where medications may be purchased at virtually any location including, for example, a gas station. Unlike in Canada, no learned intermediary would be present if these drugs were available OTC in the U.S. Also, the Canadian system provides for a free-of-charge access to the physician at any time, and the physician plays this free-of-charge learned intermediary role. Unfortunately, this is not the situation in the U.S.

From a process perspective, the manufacturer typically initiates a switch by the filing of a comprehensive NDA supplement containing data from rigorous studies, including actual use studies, label comprehension studies, together with new proposed laboratory. In this particular case no supplement has been filed. No studies have been performed. No actual OTC use or labeling comprehension studies have been conducted --

nothing that provides the appropriate information as to the likely patient health impact of an OTC switch.

The very companies who have the most knowledge about the safety and efficacy of the drugs are being given no more than 15 minutes each to inform the panel of all the issues. It is virtually impossible for us to adequately address the proposed switch in this amount of time and in the absence of guidance from the FDA as to the new criteria by which we are to make this decision.

My question to the panel is why are we doing all this? Blue Cross has publicly stated its desire to save 18 million dollars, which represents less than one percent of their operating expenses, by eliminating reimbursement for non-sedating antihistamine prescriptions and related doctor visits. And, with all due respect, we do not believe that helping an insurer improve its bottom line by 30 percent through shifting costs from its ledger to the pocketbook of consumers is a valid enough reason to turn a proven OTC process upside down.

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More importantly, a switch could prompt

unintended consequences by changing the way millions of patients suffering from allergic rhinitis are managed. While Blue Cross arguments trivialize allergic rhinitis, its diagnosis and its treatment, prominent allergists, ENTs and other specialists have spoken quite compellingly directly and through their professional associations about the potential adverse event of a switch on patient care as defined by the joint task force on practice parameters and by the allergy report which most of you are familiar with.

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These guidelines clearly highlight the first steps of a successful allergy management to be history taking, physical examination and identification of environment and occupational allergens. Further, these guidelines underscore the importance of early diagnosis, differential diagnosis, the management of coexisting or complicating medical conditions, along with patient specific education. The experts do not believe that patients are safely capable of accurately diagnosing their condition, identifying their allergy triggers, let alone determining the most appropriate course of treatment.

Frankly, no one can predict with certainty the safety consequences of suboptimal care, misdiagnosis or increased co-morbidities. And, no one can predict with certainty how the decrease in the physician patient contact will impact special populations such as pediatrics and the elderly. For example, the dose of the three non-sedating antihistamines have to be adjusted for patients with renal impairment. The doses of loratadine and cetirizine have to be adjusted for patients with liver impairment. Finally, fexofenadine is still labeled as a Category C related to pregnancy. If the experts are correct, the short-term gain to insurers as a result of a shift of medication cost to patients will definitely increase the overall healthcare burden.

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In addition, a switch of the non-sedating antihistamine class would, frankly, turn the current model of physician-patient interaction, and may I add reimbursement to the patient by the insurance company, on its head. The patient, not the physician, will have to diagnose the condition. The patient, not the physician, will have to select what medications to take and how to take them.

Finally, the patient, not the insurance company, will have to pay for the medication. I must question how this new trial and error model of healthcare benefits the patient. In trivializing the management of allergic rhinitis, are we in fact lowering the bar for other petitions seeking to switch new classes of drugs in the future? In the end, if Blue Cross has its way, not only will the physician-patient relationship be undoubtedly be weakened, but also patients will no longer be reimbursed for their medication.

Studies show that even modest increases in personal out-of-pocket costs, as projected by Blue Cross, may be a significant barrier to the choice of the optimal medication. A switch may result in increased use of the less expensive antihistamines, the very drugs which the Blue Cross contends are dangerous.

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Certainly, the Blue Cross petition does not answer these questions, nor does it provide any evidence that a switch will benefit patient health and safety.

Their petition is essentially based on two arguments. Blue Cross argues, number one, the

current sedating antihistamines available over-the-counter are, and I quote, dangerous. However, we question why Blue Cross' own formulary continues to reserve non-sedating antihistamines for patients who have either failed or are unable to tolerate over-the-counter therapy. In fact, if these products were unsafe, then the FDA would have acted decisively to address the issue rather than making decisions regarding another class of drug. If, on the other hand, as the FDA has stated, sedating antihistamines are safe as currently labeled, then there is no basis for the petition in the first place.

Blue Cross also argues that patients are being denied access to the non-sedating antihistamines because those drugs are not available over-the-counter. In fact, a vast majority of Americans have prescription drug insurance and one or more of the non-sedating antihistamines is approved on virtually every formulary in the United States. Also, Aventis and other manufacturers offer direct assistance to the uninsured and the needy. Specifically, through our patient assistance program and through sampling Aventis distributes enough treatments to treat free

of charge 1.3 million allergy sufferers every year. It is somehow difficult to understand why, as Dr. Seidman suggested earlier, an OTC switch will help the uninsured and the Medicare patients.

We certainly hope that Blue Cross will never deny access to an important medication. If Blue Cross is concerned about access and patient safety, why does it have a policy that hinders access to the non-sedating antihistamines by its own members?

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There are also regulatory and legal liability issues to consider in the United States. Until we have confidence that a switch will not harm patients we are not prepared to subject physicians, pharmacists or the company to liability claims based on a premature entry into the over-the-counter marketplace.

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In summary, shifting the diagnosis responsibility, the treatment accountability and the cost burden from managed care to the patient may have direct and indirect patient safety and public health implications. Through petitioning the FDA, Blue Cross of California is raising the

potential that the patient will be playing a risky trial and error game with their health, with their quality of life and with their money.

A switch could, in fact, change the healthcare delivery model for the 40 million Americans who suffer from allergic rhinitis. The management of their disease will switch from a physician-driven diagnosis and treatment and from a reimbursed medication to a self-diagnosis, a self-chosen treatment but also a self-payment.

It is possible that a switch may be appropriate at some point in time, but there can be no substitute for sufficient and reliable post-approval clinical experience and patient exposure data when evaluating an OTC switch. We are not there yet with fexofenadine. We believe it is premature, based on our market experience, to consider switching fexofenadine to an OTC status, and we did not find any compelling reasons to make a snap judgment and a rushed decision on switching the prescription non-sedating antihistamines to an OTC status.

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Finally, with your permission, let me address the questions the FDA posed to the panel

today. Should fexofenadine be available for OTC use? We believe this would be a premature move.

As to what concerns should be addressed prior to OTC marketing, we believe that we must continue first to assess the post-marketing data as well as conducting post-approval clinical trials to further characterize fexofenadine in a prescription environment. Additional studies have to be conducted to assess completely and comprehensively the impact of an OTC switch.

I thank you for your time and attention, and we definitely look forward to continuing to work with you and with the FDA in our ongoing efforts to improve public health. Thank you.

DR. BRASS: Thank you. We now recognize Dr. Spiegel from Schering Plough for the second response to the petition.

DR. KRENZELOK: May I ask if there is really going to be no formal response from Pfizer on this issue today?

DR. BRASS: My understanding is Pfizer was invited to participate and declined the opportunity. We have a couple of minutes during the AV period, if Aventis would be willing to answer a few questions at this point, and if there

are any panel questions for Aventis we might proceed. I would ask you to use the microphone right there. Dr. Fink?

DR. FINK: One comment and one question. My comment is that I think we should really take the cost issue out of this discussion. The consumer pays for the cost of these drugs whether it is through insurance premiums or out-of-pocket expenses. So, we are really talking about cost shifting, not cost savings, and it is inappropriate for today's meeting.

But my direct question to Aventis is if loratadine and cetirizine were granted over-the-counter status, do you envision that you would then seek over-the-counter status for fexofenadine?

DR. NADER: To directly answer this question, we did not assess, frankly, internally what will be the course of action if cetirizine and loratadine would go over-the-counter.

DR. DYKEWICZ: My question is what is the relative amount of experience with use of fexofenadine versus terfenadine? You mentioned that terfenadine had 24 million years of patient experience. What is that for fexofenadine? Also,

do you have any breakdown in terms of pediatric experience?

DR. NADER: The total experience for fexofenadine today is around 4.7 million patient years. This includes all formulations. For pediatrics it is very, very small. I would say it is in the range of probably 200,000 to 300,000 since the product has been on the market for about a year. The vast majority is actually the 60 mg b.i.d.

DR. BRASS: Dr. Ford?

DR. FORD: I am from the Harlem Lung Center at Columbia University. You mentioned a potential for a shift in the paradigm in terms of provider-patient relationships, in particular in relation to self-diagnosis. I am not comprehending how it happens because with first-generation drugs my understanding is that patients actually self-diagnose and utilize them. I am wondering how it is that this would be different with the second generation.

DR. NADER: We simply believe that one of the elements that came with the petition has to do with savings related to the direct physician cost, and we believe that if there are savings it means

that the patients will see their physicians less. Therefore, we believe that the patient relationship will be hindered to a large extent. Today we have the non-sedating antihistamines first generation available OTC. The second generation, however, are available by prescription and the physician has the opportunity to discuss the treatment with the patient. This opportunity will be lost, frankly, if all the drugs are switched to an OTC status.

DR. BRASS: We will now proceed with Dr. Spiegel's presentation.

Response to Petition by Schering Plough

DR. SPIEGEL: Thank you.

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Well, a belated good morning but good morning nonetheless. I am Dr. Robert Spiegel, Chief Medical Office and Senior Vice President of Medical Affairs at Schering Plough. I have with me today a number of other representatives from Schering Plough who are available for your questions, as well as a guest we have asked to come with us, Dr. Gary Rachelefsky, who is a practicing allergist and a past president of the American Academy of Allergy and Immunology, and a clinical professor at UCLA.

You have been asked to day to assess the appropriateness of loratadine in an OTC setting, and this morning I will be describing why this issue is actually quite complex and why we believe it raises some major issues that must be carefully addressed and review to responsibly evaluate such a switch.

Schering Plough has been involved in developing antihistamines for over forty years. And, over the last ten years we have learned a great deal about our drug, loratadine, and a great deal about the allergy patient, the U.S. healthcare system for allergy and the way loratadine is used in that system. Indeed, loratadine and the other second-generation antihistamines have played a role in redefining the disease management of allergies in the last decade. In this context, we too have thought a great deal about the appropriateness of loratadine as an OTC product, and we have concluded, and we strongly believe, that loratadine should be a prescription procedure.

This morning I am going to tell you why. In your briefing book the FDA's OTC antihistamine review team lists the OTC switch principles developed in the early 1990s. They include the

question has a vigorous risk analysis been performed. I think the answer to date is clearly no.

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The very serious issue here that requires vigorous analysis begins with the following fact: For many patients allergies are not appropriately treated without physician management. There are many different types of antihistamine users. There are patients who use them for short-term periods and patients who use them chronically. There are those with co-morbid diseases and those without. And, there are patients who use antihistamines for colds versus those who use them as part of a disease management regimen for allergies. We believe you need to think very carefully about just where on this spectrum of allergy is OTC use potentially appropriate.

Secondly, we believe it is obvious that more data and studies are necessary to appropriately evaluate a switch based on unique issues related to use. There are also many unaddressed label development and label comprehension issues raised by this proposed switch, such as what patient population does the

label address? How long should a patient dose before seeking medical attention? Should common cold use be prescribed?

For these second-generation antihistamine products, shouldn't label comprehension be demonstrated for safe and effective use? Data on these and other important issues are currently lacking from any source. It would be a very poor precedent to consider an OTC switch without such analyses.

We would ask you today to carefully consider the principles this committee and the agency have established previously for OTC marketing. Again, in the FDA's briefing document the OTC antihistamine review team summarizes the principles established in the 1990s for OTC switches. It states actual use trials and label comprehension trials may or may not be needed, depending on whether there are any unique issues related to use, warnings or directions that need to be tested prior to market. It further states the switch of a prescription drug to OTC marketing requires a review of the post-marketing safety data and a determination that a consumer can adequately use the product in an OTC setting.

In the briefing book and today the FDA reviews the intrinsic pharmacologic properties and safety of the loratadine molecule. But Rx to OTC switches raise issues beyond the simple pharmacologic toxicity of the molecule. They raise issues about the consumers who will use the product and how they will use it. We believe there are definitely unique issues in this case that, at a minimum, require that research questions be answered regarding actual use and label comprehension. Moreover, we have established that the current loratadine user likely is a different allergy patient than the current OTC user of antihistamines, and the current OTC antihistamine user may well have a different spectrum of allergies or colds than the current loratadine user.

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Finally, one must recognize that there are major cost and healthcare policy issues implicit in this OTC petition. Of course, there are financial considerations in an OTC switch. The incentive for the insurance companies is clearly economic. But an OTC switch has profound cost and, thereby, access issues for patients. This is particularly

problematic for Medicaid and the poor who may be at the greatest risk but who may well be denied access to the best available therapy if these drugs go OTC. In today's presentation I will address these issues which we believe are critical to your assessment.

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We begin today's discussion with a recognition that for many patients allergies are not appropriately treated without physician management. This is a complex patient population that includes simple as well as complicated allergy patients, some of whom have a debilitating chronic condition or potentially life-threatening co-morbidity such as asthma.

Our position against OTC switch is based on three medical findings. First, prescription status may be necessary to protect and optimize public health. Given the current prevalence of allergies and what has been described as an asthma epidemic in the United States, given the complexity of allergy and co-morbid diseases, and given the increased recognition of patient safety issues related to overuse, under-use and misuse of medications, now is not the time to drive allergy

patients further away from their physicians.

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In order to improve overall public health and the delivery of quality health care, the U.S. healthcare system has seen a major change in approach over the last ten years. This has involved an emphasis on evidence-based medicine and guideline-driven practice, and this is especially true in the area of allergies and asthma. Guidelines have been developed in this area which include guidelines from the NHLBI, the task force for allergic disorders, the WHO, recently issued ARIA and GENA guidelines.

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All of these guidelines is the area of allergy emphasize the following approach for optimum outcomes. Here is what occurs when a learned intermediary is involved in the process. It begins with an evaluation by the physician to differentiate allergic disorders from other diseases. There is then an attempt and a careful analysis to uncover previously unsuspected allergens and to assess important co-morbid conditions that might exist. It also includes an environmental assessment of whether there are

allergens in the patient's home environment, work environment or school environment that might need to be eliminated. Many patients don't need any pharmacologic intervention but they need to change the environment in which they are operating. And, for selected patients antigen testing is appropriate. This is followed by an assessment of the need for pharmacologic therapy which can include antihistamines, decongestants, nasal steroids, for appropriate patients' immunotherapy and, of course, when appropriate prescriptions for co-morbid conditions. Then it ends with careful follow-up, reassessment and compliance management.

OTC status with attendant self-diagnosis and self-management would directly undermine this physician-managed approach. The insurance companies see a physician visit as a cost item. We see it as a critical point of care in the disease management process. As a physician, I would ask you isn't it obvious that OTC status can only produce suboptimal outcomes as compared to this system?

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Now let's turn to the second reason why for many patients allergies are not appropriately

treated without physician management. That is, the safety profiles of second-generation antihistamines are well recognized in a prescription setting but they are not fully known in a U.S. OTC system. The FDA has reviewed the intrinsic pharmacologic safety of the loratadine molecule, but as physicians, pharmacists and healthcare professionals know, an Rx to OTC switch raises safety issues beyond the simple pharmacologic toxicities of the molecule. They raise issues about the consumers who use the product.

We know loratadine is a very effective and safe product when used as a prescription product under a physician's supervision. But we don't know what that profile will look like in a U.S. OTC setting.

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We don't know how often it will be inappropriately used to treat colds. We don't know how often patients will overdose or under-dose. Specifically, many patients dose their current OTC antihistamines until they feel sedation. Will they take a non-sedating antihistamine in excess in a similar pattern? Moreover, no current OTCs are currently once a day. Most are twice a day or more

frequent. How often will patients dose their loratadine outside of labeling? I also ask what will happen when this occurs with products that contain 240 mg of pseudoephedrine? How many patients will experience exacerbation of untreated or unrecognized co-morbidities? Finally, now often will patients have adverse outcomes as a result of delay in seeking medical care?

These issues cannot be answered by simply looking at the results of a spontaneous AE reporting system in a post-marketing drug surveillance database. These are notoriously ineffective for addressing such questions.

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Now let's turn to the third reason why for many patients allergies are not appropriately treated without physician management. Allergies are frequently chronic, complex diseases with serious co-morbidities, and the understanding of these diseases has changed significantly in the last ten years. Allergies are not just a runny nose.

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I mentioned at the beginning of my talk that we have learned a great deal about allergies

in the last ten years, and most of that is different from what we used to think. We have learned that allergies are frequently chronic and complex for many patients; that they are very frequently associated with co-morbid conditions and these can affect up to 40 percent of allergy patients, and the co-morbidities can be serious and their incidence and outcome can be affected by the management of allergies. And, allergies are a chronic condition that requires long-term management, not just episodic symptomatic treatment. Moreover, allergies have a particularly large impact on children and adolescents.

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It has been widely noted in the lay press, as captured in this cover story from a year ago, that allergies are widespread in the United States. Let me spend a moment speaking particularly about the importance of one of the most common co-morbidities of allergies -- asthma.

Allergies have been estimated to affect 40 to 50 million Americans. Asthma affects 50 million Americans and 4.8 million children. Of concern, asthma prevalence has been documented to have increased 75 percent during the period of 1980 to

1994, and during this period asthma deaths increased from a rate of 11.5 per million to 18 per million, resulting in 5500 deaths per year.

Given the seriousness of this public health problem, HHS has just sent out a directive to all state Medicaid agencies recommending the implementation of disease management programs for asthma. As I stated earlier, now is not the time to drive patients further away from the physician.

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The link between allergies and asthma is now widely recognized, and 78 percent of asthma patients have nasal symptoms and 38 percent of allergic rhinitis patients have been noted to have asthma. We know from our own experience that in the year 2000 three million Claritin scripts were co-prescribed with prescriptions for asthma medications, affecting approximately 1.2 million patients with asthma.

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A number of studies have examined the relationship between treatment of allergies and asthma outcomes. It has been noted that treating allergic inflammation in the nose can induce asthma symptoms and lower airway hyper-responsiveness. It

has also been documented that asthmatic patients with allergic rhinitis have higher medical costs, and in one study cited here, a longitudinal study was conducted in 783 students who were identified while they were in college and then followed for 20 years. Resolution of allergic rhinitis symptoms correlated with improvement of their asthma, and worsening of their rhinitis was associated with the persistence of asthma. So, there is a very real reason to believe that suboptimal or inadequate care of allergies might result in worsening outcomes for patients with this major co-morbidity.

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The previous slides reviewed some of the reasons most allergists and primary care physicians now treat allergies and antihistamines in a new way. First-generation antihistamines tend to be used for short-term episodic use. They tend to be used for simple symptom relief in relatively simple allergy patients. It is unknown what amount of co-morbidity exists in these patients, but we do know that over half of the use of the current OTC antihistamines is for use in the treatment of cold symptoms, not relief of allergy.

In contrast, the second-generation

antihistamines tend to be used for long-term chronic use. Again, in our own data the average use of Claritin is for more than 60 days. Second-generation antihistamines tend to be used for disease management for complex patients. We know that they frequently have co-morbidities and, as was noted earlier this morning, these products are not effective for colds due to their lack of anticholinergic activity.

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Finally, there is a major public health risk implicit in this switch proposal. Any reasonable assessment of likely OTC pricing leads to the conclusion that millions of patients, in particular poor and Medicaid patients, will be unable to afford the second-generation products as OTCs. Many other patients who now have insurance coverage will begin to make inferior medical decisions based on their out-of-pocket costs, not based on what is the best available medical therapy.

Just as the medical issues are not simple, so too the economic and directly related access issues are complex. The Blue Cross petition implies that as a result of a switch currently

available first-generation OTC antihistamine use will decrease and that access to second-generation antihistamines will increase and solve the purported problems of the first generation. This is not so simple. We believe this OTC switch proposal represents plain cost shifting that will decrease access and may reverse the current U.S. trend.

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Here are some real facts to consider. In the U.S. today the first-generation products share of total dosage days has been steadily decreasing and in the year 2000 comprised only 17 percent of the antihistamine market. In contrast, in the current Canadian marketplace where all antihistamines are OTC, the first generation have a 23 percent market share and their share continues to rise slightly every year. So, there are often unintended consequences of well-intentioned actions. Market forces in an OTC marketplace in the U.S. could well drive a return to growth in the use of first-generation products.

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Let me conclude by restating that Schering believes we have learned a great deal about

allergies, and their complexities, and about the different types of allergy patients. We are convinced that loratadine is most appropriately used as a prescription product.

In my presentation today I have focused on several issues that should convince you that there are, indeed, many unique issues related to use in this situation. The fact that such a switch will immediately affect tens of millions of patients should be of concern and requires careful thought, more study and certainly more data than have been provided to date.

We have provided some insight into the very real differences between the way the first and second-generation antihistamines are used. First-generation antihistamines are used primarily as short-term acute therapy. They are used more often for relief of colds than for allergy relief. Second-generation antihistamines are used more as part of a chronic disease management approach to allergies, and they are generally used for more than 60 days.

Given these unique and complex issues in the allergy patient, as well as the potential seriousness of allergies and their complications,

it would certainly seem appropriate to ensure that the FDA OTC switch criteria and the rigor that has been applied over the last decade to OTC switches be applied here. In the FDA's briefing book the OTC antihistamine review team reviews the so-called PET principles evolved in the 1990s to assess OTC switch proposals. These are the types of issues and studies routinely looked to in a sponsor's application for an OTC switch. Clearly, you have not been provided with sufficient data to address these issues.

Labeling must be developed and tested for many of the issues raised here. Finally, if there were ever a setting that would require an actual use study, this would be the one. Actual use trials are designed to assess how consumers actually use the product in an OTC setting. It provides a test of the consumer, not the drug. It might also provide a perspective on outcomes under the care of a learned intermediary versus real data on outcomes when patients are on their own.

It has been stated today, and it will be stated later this afternoon, that patients can self-diagnose and self-treat allergies, but where is the data? Actual use studies have been done for

almost all recent OTC switch proposals. Why wouldn't they be expected in this case? Interestingly, in the case of ketaprofine an actual use study established that over 45 percent of the subjects took more drug than the labeled dose. Shouldn't we know similar results for loratadine before recommending a switch?

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In closing, let me leave you with this thought, a key issue in determining whether OTC status would jeopardize public health is obviously safety. As you are aware, no drug is simply safe or not safe. When FDA approves a drug it is determining that its overall benefit to risk index is appropriate for its intended use. In the case of loratadine, we know its benefit to risk ratio is very positive in the prescription setting under a physician's management. We don't have sufficient data about how the benefit to risk equation might shift in the U.S. OTC system and, in fact, there are reasons to believe that benefits could decrease while risks could increase. Decreased benefit could result from one-time episodic use versus daily use; from indiscriminate use in colds; from use without physician assessment and management;

and from patient self-treatment without identification and elimination of obvious environment allergens. Increased risk could result from exacerbation of untreated or unrecognized co-morbidities, inadvertent overdosing or delays in seeking medical care.

These are the questions in the equation that we would ask you to consider and evaluate whether you really have adequate information today to consider placing millions of patients at potential risk of diminished efficacy, as well as increased risk as they struggle to treat their allergies. Thank you.

DR. BRASS: Thank you. Because of the hour, we are going to hold the many questions for the manufacturers until this afternoon, and at this point take our break so that we can reconvene at 10:15 promptly to begin the open public hearing. Thank you.

[Brief recess]

Open Public Hearing

DR. BRASS: I will remind all of the public speakers to please include a conflict of interest statement and any sponsorship for their visit as they begin their remarks, and to please

mind the time limit as we have a full agenda. Dr. Schenkel?

DR. SCHENKEL: Good morning. My name is Dr. Eric Schenkel, and I am Director of the Valley Allergy and Asthma Treatment Center in Easton, Pennsylvania, and Director of Valley Clinical Research Center in the same city.

Although I am a consultant and a clinical investigator for a variety of pharmaceutical companies, including the three companies mentioned here, I am here on behalf of my patients. I am a practicing allergist. I am down in the trenches every day and, believe me, my patients are extremely concerned and, granted, very upset about the issues that have been presented here and what has been presented in the media. I am also very concerned about this potential switch of very effective prescription drugs to an over-the-counter status.

I would imagine there are many allergy sufferers in this room. As you have heard upwards of 40 to 50 million Americans suffer with some form of allergic disease and their co-morbidities. And, as we heard before, no one really ever dies of an allergic rhinitis or runny nose but they make